



NDA 19-537/S-030/S-031/S-033
NDA 20-780/S-001/S-002/S-003/S-004

Food and Drug Administration
Rockville MD 20857

SEP 17 1998

• Bayer Corporation
Attention: Ann Marie Assumma
Associate Director, Regulatory Affairs
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516-4175

Dear Ms. Assumma:

Please refer to your supplemental new drug applications (NDA) dated October 1, 1997, October 15, 1997, April 16, 1998, and August 12, 1998 received October 2, 1997, October 16, 1997, April 16, 1998, and August 13, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin) Oral Suspension.

We acknowledge receipt of your submissions dated September 14, and September 16, 1998.

These supplemental new drug applications provide for the following changes to the label:

1. Addition of text and a chart in the **CLINICAL PHARMACOLOGY** section to read as follows:

“A 500-mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750-mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg over 60 minutes every 8 hours. A 750-mg oral dose results in a C_{max} similar to that observed with a 400-mg I.V. dose. A 250-mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.”

Steady-state Pharmacokinetic Parameter Following Multiple Oral and I.V. Doses				
Parameters	500 mg q12h, P.O.	400 mg 12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC(ug■hr/mL)	13.7 ^a	12.7 ^a	31.6 ^b	32.9 ^c
C _{max} (ug/mL)	2.97	4.56	3.59	4.07
^a AUC 0-12h	^b AUC 24h=AUC _{0-12h} x2 ^c AUC 24h=AUC _{0-8h} x3			

2. Addition of the term “taste loss” under the category **SPECIAL SENSES** in the **Post-Marketing Adverse Events** subsection of the **ADVERSE REACTIONS** section of the labeling.
3. Addition of information pertaining to the use of Cipro in Cystic Fibrosis patients to the **Pediatric Use** subsection of **PRECAUTIONS** section to conform with the Cipro Tablet and I.V. labeling. The second and third paragraphs of the **Pediatric Use** subsection of **PRECAUTIONS** should read as follows:

“Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double- blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime I.V. 50mg/kg/dose q8h and tobramycin I.V. 3mg/kg/dose q8h for a total of 10-21 days. Patients less than 5 years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in the comparison group (8%). Other adverse events were similar in nature and frequency between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the Ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. One of the sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other

abnormalities eight months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitely determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease processes."

4. Revision to the **Information for Patients** subsection of the **PRECAUTIONS** Section of the labeling. The first bullet now reads:

- "that ciprofloxacin may be taken with or without meals. The preferred time of dosing is two hours after a meal. Patients should be advised to drink fluids liberally and not take antacids containing magnesium, aluminum, or calcium, products containing iron, or multivitamins containing zinc. Ciprofloxacin should not be taken concurrently with milk or yogurt alone, since absorption of ciprofloxacin may be significantly reduced. Dietary calcium as part of a meal, however, does not significantly affect ciprofloxacin absorption."

5. Revisions requested by the FDA in letters dated May 28, 1998 and June 17, 1998 have been incorporated. The revisions are as follows:

In the **WARNINGS** section of the labeling, the sentence "**THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN CHILDREN, ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (SEE-PEDIATRIC USE, PREGNANCY AND NURSING MOTHERS SUBSECTIONS.)**" is revised as follows:

"THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing Mothers subsections.)"

In the **PRECAUTIONS** section **Information for Patients** subsection, the labeling is revised to include the following statement at the end of the advise list:

"Patients should be advised that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking the drug if there is a history of this condition."

6. Deletion of the statement "**Caution: Federal (USA) Law prohibits dispensing without prescription.**" This now reads: "**Rx Only.**"
7. Other minor editorial changes such as changes in capitalization.

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We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the draft labeling dated September 16, 1998. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 19-537/S-030/S-031/S-033 and 20-780/S-001/S-002/S-003/S-004. Approval of this submission is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of that labeling may be required.

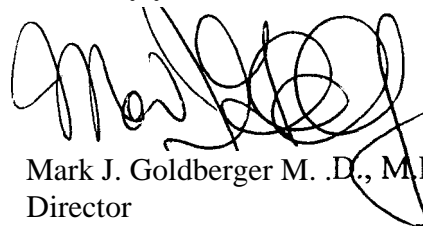
Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to those NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Mary Dempsey, Project Manager, at 301-827-2127.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Mark J. Goldberger', is written over the printed name and title.

Mark J. Goldberger M. D., M.F.
Director
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research